2011 Indiana Carbapenem-resistant *Enterobacteriaceae* Survey

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Antibiotic Resistance

Antibiotic resistance is a global issue that has significant impact in the field of infectious diseases. It has been recognized for several decades that up to 50% of antibiotic use is either inappropriate or unnecessary. Antibiotics are the only drug where use in one patient can impact the effectiveness in another. Improving antibiotic use is a public health imperative.

Klebsiella pneumonia and *Escherichia coli* which are included in the family of Gram-negative bacteria known as *Enterobacteriaceae* are epidemiologically and clinically important organisms due to their level of antibiotic resistance. The carbapenem-resistant strains of these organisms are referred to as carbapenem-resistant *Enterobacteriaceae* (CRE). Carbapenem-resistant *Klebsiella pneumonia* (CRKP) is the CRE species most commonly seen in the United States. Sometimes these drug-resistant bacteria are referenced to the *Klebsiella pneumoniae* carbapenemase (KPC), the enzyme that inactivates carbapenems. This KPC enzyme is also present in some strains of *Escherichia coli*. The gene that confers this resistance pattern is contained on plasmids, which are highly mobile and very easily spread from one bacterial cell to the next. Since these cells are harbored in the gut, the plasmids are potentially transferrable to multiple coliforms. Healthcare-associated infections reported to the CDC showed the overall prevalence of KPC rising from less than one percent in 2000 to eight percent in 2007.

Healthcare providers should be concerned about CRE infections as they are associated with high rates of morbidity and mortality, serious treatment challenges, increased length of stay, and increased cost. The frequent movement of patients between acute and long term care provides the opportunity for transmission of these resistant organisms. Aggressive communication between both acute and long term care is important so that appropriate intervention can take place.

CRE are an emerging, important healthcare challenge, resistant to almost all current available antibiotics. Pharmaceutical companies are no longer involved in the development of antibiotics. From 1983-1987, sixteen new antibiotics were approved by the US Food and Drug Administration (FDA). However, from 2008-2011 only two new antibiotics were approved and neither addressed the issue of resistance. In 1990, nineteen companies developed antibiotics, presently only four produce them. It will be five to ten years before new antibiotics are available to treat resistant organisms.

Given this lack of new antibiotics to treat CRE infections an aggressive infection control strategy is critical to prevent the transmission of these resistant organisms. Early detection and implementation of necessary strict infection control measures can prevent carbapenem-resistant organisms in healthcare facilities from becoming a more significant threat to patients.

Microbiology laboratories in all acute care facilities must implement enhanced protocols to detect carbapenemase production in *Enterobacteriaceae.* When these organisms are identified the laboratory must immediately alert acute and long term care infection preventionists. This will allow important control measures to be implemented including vigorous hand hygiene practices, contact precautions, and minimizing the use of devices. Further detailed guidance from the CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC) which includes recommendations for active surveillance, the review of microbiology results for past 6-12 months and the charting of staff or patients is located at

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5810a4.htm and referenced in the Table provided in the Resources section of this document.

To slow the evolution of resistance healthcare providers must focus on antibiotic stewardship. Stewardship programs will enforce pathogen-directed therapy and short-course treatment. In a recent study the CDC reported that exposure to a carbapenem antibiotic increased a patient's risk of getting an infection with a carbapenem-resistant strain by 15 times. When ordering antibiotics healthcare providers are encouraged to appropriately select antibiotics including specific dose, duration, route and indication. Antibiotic use should be reassessed after 24 to 48 hours to review susceptibility results and determine if treatment can be altered. Further detailed guidance describing the development an antibiotic stewardship program from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) is located at http://cid.oxfordjournals.org/content/44/2/159.full

The Indiana State Department of Health (ISDH) strives to heighten awareness of the challenges posed by antibiotic resistance and specifically CRE. The combination of a comprehensive infection prevention program and effective antibiotic stewardship will minimize the emergence and transmission of CRE in Indiana.

In order to better understand the current healthcare facility infection control practices and CRE detection practices in Indiana, the ISDH Surveillance and Investigation Division (SID) and the ISDH Laboratory partnered to develop surveys that were sent to infection preventionists and clinical laboratories. The results from these surveys are summarized below.

Infection Preventionist/CRE Prevalence Survey Results

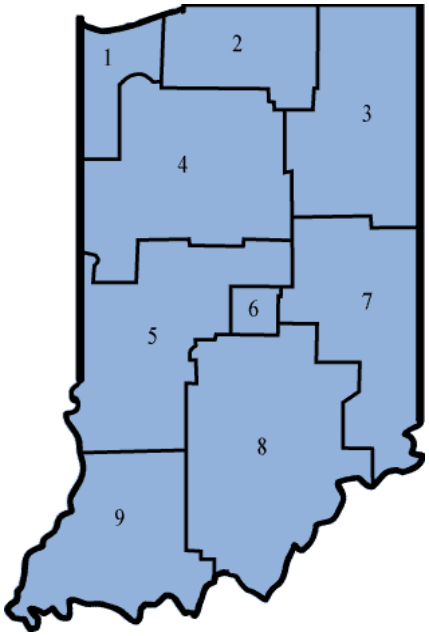
In an effort to better understand the current burden of CRE infection in Indiana's healthcare facilities, infection preventionists (IPs) from around the state were surveyed. A 10-question survey was sent to members of APIC-Indiana (Association for Professionals in Infection Control and Epidemiology) members and 40 responses were received.

Respondents were asked to specify in which of the nine APIC-IN regions their healthcare facility was located; responses were received from all nine regions.

	Number of IPs responding	Percentage of IPs responding
Region 1	5	12.5%
Region 2	3	7.5%
Region 3	7	17.5%
Region 4	3	7.5%
Region 5	6	15%

Region 6	7	17.5%
Region 7	3	7.5%
Region 8	1	2.5%
Region 9	5	12.5%

Indiana APIC Regions



The IPs surveyed work in healthcare facilities of various sizes, ranging from smaller facilities with fewer than 50 beds to larger hospitals with more than 200 beds.

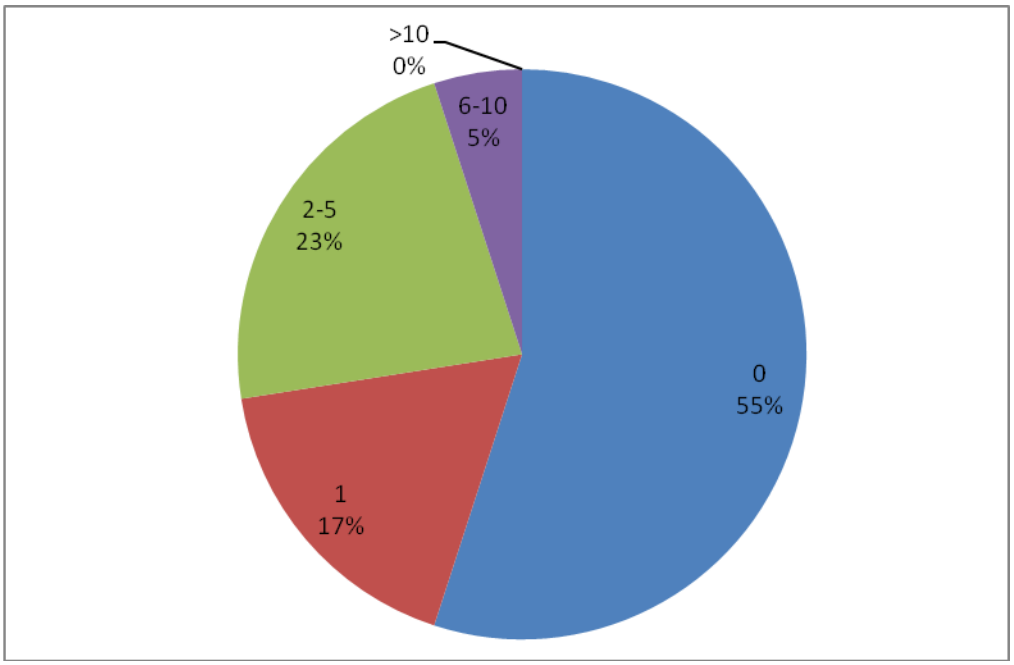
HCF Bed-size	Number of IPs responding	Percentage of IPs
0-50	11	27.5%
51-100	7	17.5%
101-200	8	20%
>200	14	35%

We were interested in determining where CRE testing was being conducted. Of the 40 IPs who responded, 62.5% reported that their healthcare facility had a laboratory that performed CRE testing. The IPs were also asked how their facility's laboratory responded to a reported CRE case. They were allowed to choose all options that applied. The most common responses were that the laboratory notified the IP, the nursing station, and/or the healthcare provider. Only 7.5% had a process for flagging the patient chart, and 15% reported that their laboratory took no action upon receiving notice of a CRE case.

Action taken if CRE is reported to Lab	Percentage of Labs
Notify IP	67.5%
Notify Nursing Station	52.5%
Notify Healthcare Provider	40%
Flag Patient Chart	7.5%
No Action Taken	15%

The majority of IPs surveyed (72%) stated that their HCF reported 1 or fewer positive CRE cases per month. Approximately 23% reported 2-5 cases per month, 5% stated that they had 6-10 cases, and no one reported more than 10 cases per month.

How many positive CRE reports does your HCF identify each month?

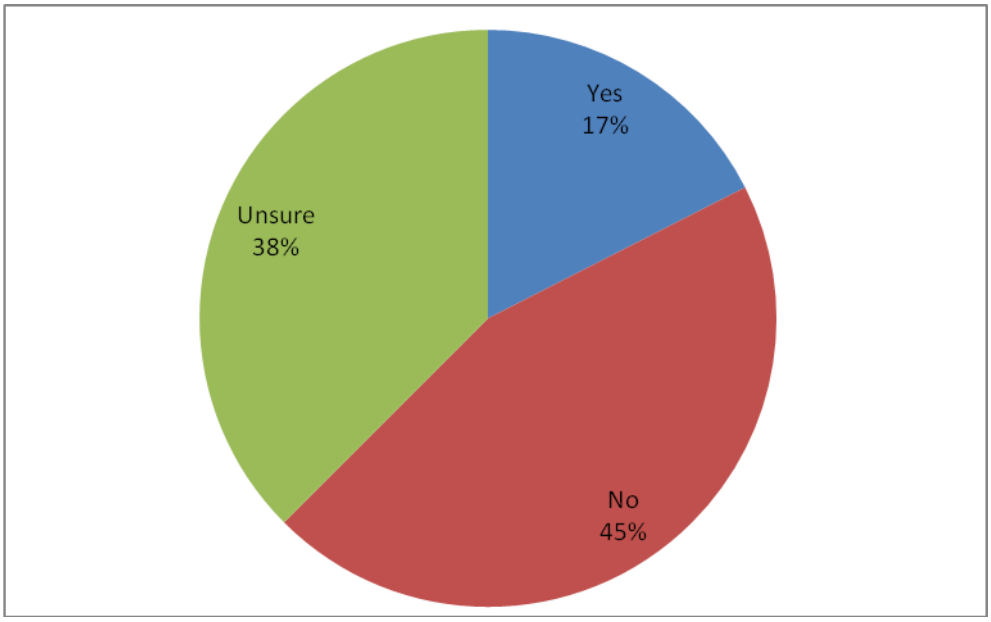


Most IPs (87.5%) were aware of, and are practicing, the CDC's infection prevention and control guidelines for CRE. These guidelines are a set of recommendations from the CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) for controlling CRE in inpatient facilities. Only five respondents (12.5%) were not practicing these guidelines. In addition to the CDC's recommendations, 80% of IPs stated that their facility also has a notification system in place to alert other facilities when a patient with CRE is transferred out of their facility.

Finally, 45% of IPs did not think that CRE should be reported to ISDH, 17.5% said yes it should be reported, and 37.5% were unsure. Details to the IPs answers provided a variety of responses. Among those IPs that thought that CRE should be reportable, one said that carbapenem-resistance poses a "potentially serious public health issue" and others thought that we need to "grab onto these before they spread any faster."

IP's that disagreed with CRE reporting, many felt that since "other MDROs are not reportable, they shouldn't be required to report CRE". Some IPs also had concerns about "what ISDH would be doing with the data" and "what the benefit of reporting CRE" would be. Some also stated that they were already burdened with disease reporting and that they don't have enough time to perform the essential prevention aspects of their jobs.

Should the detection of CRE isolates be reported to ISDH?



Indiana Sentinel Laboratories CRE Testing Capacity Survey Results

The ISDH Laboratory recognizes that Indiana's sentinel laboratories play a significant role in CRE surveillance and control measures. Therefore, in order to better understand CRE testing capacity, the ISDH Laboratory surveyed sentinel laboratories about general antimicrobial susceptibility testing (AST) and specifics regarding CRE testing. The following report profiles the results from this survey and highlights recommendations from the CDC as well as specifics about AST breakpoints.

The CRE Survey sent out by the ISDH Lab Outreach Team via the ISDH LabInfo e-mail list received 37 responses. Of these 37 labs, 93% (36) report performing AST on site.

Automated systems used for AST	**Percentage of Labs**
BD Phoenix	6%
Microscan	49%
Vitek/Vitek 2	54%
Other	3%
No automated systems are used to perform AST.	0%
Non-automated methods used for AST	**Percentage of Labs**
Disc diffusion	33%
Agar diffusion	3%
Tube/Macrodilution	0%
Microdilution	8%
E-test	28%
Other	3%
No non-automated methods are used to perform AST.	53%

However, only 69% of the laboratories performing AST on-site report their automated testing is programmed to identify or flag CRE or other carbapenem-resistant bacteria. The antibiotics that laboratories use to flag potential CRE include Cepahlosporin subclass III, ertapenem, meropenem, and imipenem.

When programming the susceptibility breakpoints for these antibiotics, laboratories either explicitly refer to standards issued by CLSI or they use automated systems that have already been set to meet specific CLSI guidelines. The most recent CLSI guidelines, M100-S21, were issued in January 2011. However, the FDA does not yet recognize these most recent breakpoints. Therefore, the manufacturers of automated testing systems have not been able to update their systems to reflect these changes.

M100-S19 was published in January, 2009 and is still used by 32% of laboratories. M100-S20 was published in January, 2010 and is used by 21% of laboratories. M100-S21 is the most recent version and was published in January, 2011 and is used by 37% of laboratories.

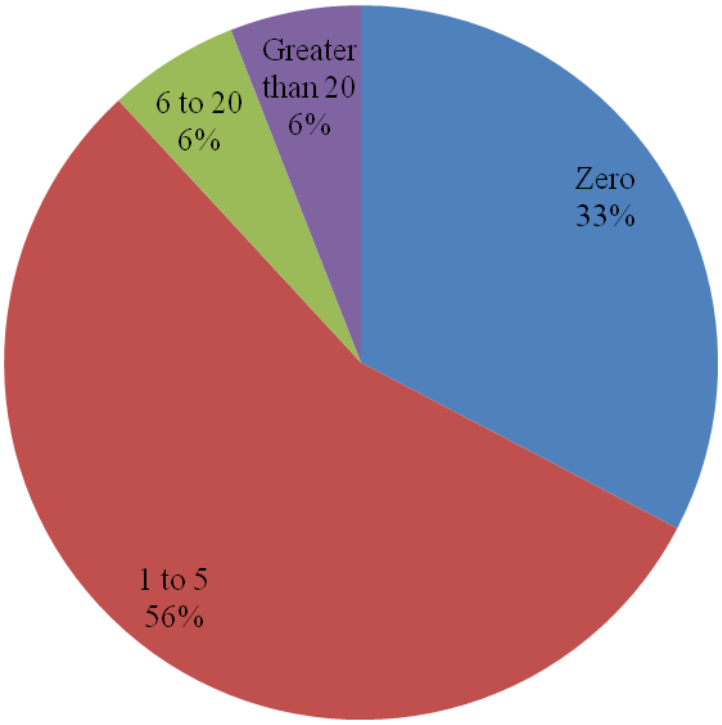
Among labs that reported using older CLSI standards (M100-S19 or M100-S20), 90% reported that the reason their laboratory had not implemented the newest standards (M100-S21) was lack of FDA approval for the newest breakpoints. Other reasons cited include unavailability of the current CLSI document (30%) and difficulty understanding.

Once a potential CRE has been flagged, 37% of laboratories perform no additional testing. Another 37% report performing a Modified Hodge Test (MHT) and the remaining 26% send potential CRE to a reference laboratory for confirmation. No laboratories reported confirming CRE identification with disc diffusion, broth microdilution, E-test, or PCR.

It is important to note that if CLSI guidelines *other* than M100-S21 are used, then laboratories should perform **both** an initial screening test and a MHT. However, if laboratories are using the new interpretive criteria contained in M100-S21 then MHT are no longer necessary. Despite these guidelines, responding laboratories using older CLSI guidelines do not perform MHTs.

Reason MHTs are not performed	**Percentage of Labs**
Lack of materials	42%
Lack of training	58%
Lack of personnel	25%
Lack of funding	33%

Number of CRE Isolates Identified Per Quarter



E. coli and *K. pneumonia* are the most commonly identified CRE. Greater than 80% of laboratories reported having never identified Proteus, Salmonella, or Morganella species as CRE organisms. Enterobacter and Serratia have been identified as CRE in Indiana, although not by many laboratories.

Action performed if a CRE isolate is identified	**Percentage of Labs**
Notify Infection Prevention Department	76%
Notify nursing station	35%
Notify physician	41%
Notify physician and make recommendations for antibiotic treatment changes	7%
Notify public health department	14%
Notify public health laboratory	10%
No further action	10%

Although CRE are not currently required to be reported to ISDH or the ISDH laboratory, this option is being considered during the upcoming round of Communicable Disease Rule revision in 2012. However, Marion County Health Department has requested that all CRE identifications in Marion County be reported to them.

The majority of laboratories polled (79%) reported that the infection control and nursing staff at their facility are aware of the healthcare implications of CRE infections and associated infection control measures. At 62% of labs, respondents were able to confirm that someone at their facility reviews clinical susceptibility data as a means to monitor patients for possible CRE infection/colonization.

Of the 28% of laboratories that think CRE should be reportable, the general concensus was that they are important for epidemiological purposes. As one respondent notes, “we do not yet have a handle on how serious of an issue this could be…until we kow how transmissible [CRE] are, we need to do all levels of surveillance and monitoring.” In addition, surveillance and disease tracking enables the spread of CRE to be contained.

Among those that responded “no” or “unsure” to the question of whether CRE isolates should be reportable (17% and 55% respectively), a common theme was that ESBLs, VRE, and MRSA isolates are not reportable so why would CRE be treated any differently. Many also acknowledged the serious infection control implications of CRE, but wondered what the relevance was to public health and what public health officials would be likely to do with this information if it was made reportable.

In the final comments from sentinel laboratories, several acknowledged the challenges of monitoring and identifying modes of antibiotic resistance and requests were made for additional education. The ISDH Laboratory recognizes these needs and is working with the ISDH SID, the CDC, and APHL to address them.

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CRE Resources

1. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5810a4.htm

2. http://www.cdc.gov/hai/
3. http://www.infectiousdiseasenews.com/print.aspx?id=70587
4. http://www.medscape.com/viewarticle/713709?src=mp&spon=24&uac=96567PY
5. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5937a4.htm?s_cid=mm5937a4_w
6. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5924a5.htm?s_cid=mm5924a5_w
7. College of American Pathologists (CAP) 2012 Survey catalog Breakpoint Implementation Tool (M100-S21) http://www.cap.org/apps/docs/proficiency_testing/2012_surveys_catalog.pdf
8. http://www.medscape.com/viewarticle/733113
9. http://www.medscape.com/viewarticle/735068
10. http://www.journals.uchicago.edu/doi/pdf/10.1086/510393
11. http://www.cdc.gov/getsmart/healthcare/?s_cid=dhqp_002

BOX. Infection prevention and control guidance for carbapenem-resistant *Enterobacteriaceae* (or carbapenemase-producing *Enterobacteriaceae*) in acute care facilities — CDC and the Healthcare Infection Control Practices Advisory Committee

Infection Prevention and Control

- All acute care facilities should implement contact precautions for patients colonized or infected with carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenemase-producing *Enterobacteriaceae*. No recommendation can be made regarding when to discontinue contact precautions.

Laboratory

- Clinical microbiology laboratories should follow Clinical and Laboratory Standards Institute guidelines for susceptibility testing (*1*) and establish a protocol for detection of carbapenemase production (e.g., performance of the modified Hodge test).
- Clinical microbiology laboratories should establish systems to ensure prompt notification of infection prevention staff of all *Enterobacteriaceae* isolates that are nonsusceptible to carbapenems or *Klebsiella* spp. or *Escherichia coli* isolates that test positive for a carbapenemase.

Surveillance

- All acute care facilities should review clinical culture results for the preceding 6–12 months to determine whether previously unrecognized CRE have been present in the facility.
  - If this review identifies previously unrecognized CRE, a point prevalence survey (a single round of active surveillance cultures) should be performed to look for CRE in high-risk units (e.g., intensive care units, units where previous cases have been identified, and units where many patients are exposed to broad-spectrum antimicrobials).
  - If this review does not identify previously unrecognized CRE, monitoring for clinical infections should be continued.
- If CRE or carbapenemase-producing *Klebsiella* spp. or *E. coli* are detected from one or more clinical cultures **OR** if the point prevalence survey reveals unrecognized colonization, the facility should investigate for possible transmission by:
  - Conducting active surveillance testing of patients with epidemiologic links to a patient with CRE infection (e.g., patients in the same unit or who have been cared for by the same health-care personnel).
    - Continue active surveillance periodically (e.g., weekly) until no new cases of colonization or infection suggesting cross-transmission are identified.
    - If transmission of CRE is not identified after repeated active surveillance testing, consider altering the surveillance strategy by performing periodic point prevalence surveys in high-risk units.
  - In areas where CRE are endemic, an increased likelihood exists for importation of CRE, and the procedures outlined might not be sufficient to prevent transmission. Facilities in such areas should monitor clinical cases and consider additional strategies to reduce rates of CRE as described in the 2006 Tier 2 guidelines for management of multidrug-resistant organisms in health-care settings (*2*). Recommendations for rate calculations have been described previously (*3*).

References

1. Clinical and Laboratory Standards Institute. 2009 performance standards for antimicrobial susceptibility testing. Nineteenth information supplement (M100-S19). Wayne, PA: Clinical and Laboratory Standards Institute; 2009.
2. CDC, Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in healthcare settings, 2006. Atlanta, GA: US Department of Health and Human Services, CDC, Healthcare Infection Control Practices Advisory Committee; 2007. Available at http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroguideline2006.pdf.
3. Cohen AL, Calfee D, Fridkin SK, et al. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. Infect Control Hosp Epidemiol 2008;29:901–13.